REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116 because the Amendment places the application in condition for allowance for the reasons discussed herein; does not raise any new issue requiring further search and/or consideration as the amendments amplify issues previously discussed throughout prosecution; does not present any additional claims; and places the application in better form for an appeal should an appeal be necessary. The Amendment is necessary and was not earlier presented because it is made in response to arguments raised in the final rejection. Entry of the Amendment is thus respectfully requested. As correctly indicated in the Office Action Summary, claims 88-101 are pending in the instant application.

I. Applicants' Information Disclosure Statement of June 4, 1999

Applicants respectfully resubmit the PTO-1449 form filed with the U.S. Patent and Trademark Office on June 4, 1999, attached hereto. The citations which were not initialed by the Examiner have been amended to contain all missing information. Applicants respectfully request that the Examiner consider these references at this time.

II. Rejections under 35 U.S.C. § 103

Claims 88-101 are rejected under 35 U.S.C. § 103(a) for being unpatentable over Wang *et al. Yaoxue Xuebao (Acta. Pharm. Sinica)* 27, 178-184, 1992 (Wang I) and Huang *et al.*, *the Alkaloids,* Vol.XXII 157-225, 1984, in view of Wang *et al. Yaoxue Xuebao (Acta. Pharm. Sinica)* 27, 173-177, 1992 (Wang II).

Wang I is cited for purportedly disclosing the tetrahydrofuran and tetrahydropyran esters of cephalotaxine. Huang *et al.* is cited for purportedly

disclosing the process for hydrolyzing the cephalotaxine alkaloids and the synthesis of the acid components. Wang II is cited for purportedly disclosing a process for cyclizing an open chain acid bearing a CTX group to the corresponding tetrahydrofuran compound.

To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See* *In re* Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the art cited by the Examiner, alone or in combination, does not suggest the claimed invention, let alone that the claimed compounds could be created with a reasonable expectation of success.

Specifically, Applicants submit that it is chemically impossible for the skilled artisan to create the compounds of the claimed invention using the disclosures of the cited references. Huang et al. discloses the synthesis of the linear sidechain

when a free alcohol function is present. Wang I discloses harringtonine derivatives which exhibit antitumor activity.

Wang II discloses two sequences which respectively refer to two different herringtonine derivatives, which are esters of cephalotaxines. Wang II also dicloses that the two sequences confirm the structure of natural herringtonines isolated from *cephalotaxus fortunei*. The first sequence involves the coupling of a linear sidechain (an acid) with the alkaloid moiety to obtain a harringtonine derivative. The Reformatsky reaction used for the coupling results in a mixture of epimers 1 and 1'. (*See* Exhibit 1). The second sequence involves the cyclization of the linear sidechain of a harringtonine derivative where the linear sidechain includes a free alcohol group. This second sequence is not a continuation of the first sequence, and does not demonstrate the same transformation of 1 to 2, as in the first sequence.

The Office Action asserts that the skilled artisan would have been motivated to combine the above references to obtain the claimed invention because the skilled artisan would have expected the analog starting materials and reactants to react similarly. Applicants respectfully submit that this is not the case for the following three reasons.

First, Applicants submit that it is impossible to synthetize compound 2 of Wang II starting from cephalotaxine and from another acidic linear sidechain. The Reformatsky reaction on the ketoester of the cephalotaxine is impossible when the linear sidechain contains a free hydroxyl. Epimer 1 cannot be obtained if another acid reactant is used in place of the acid reactant disclosed in Wang II. For this

reason alone, the combination of Wang I and Wang II cannot result in the claimed invention.

Second, if the skilled artisan tries to couple a sidechain bearing no alcohol function with the alkaloid moiety, a mixture of Epimer 1 and Epimer 2 as disclosed in Wang II would result. This compound cannot be functionalized in order to replace the H with an OH. Thus, this method of obtain the harringtonine derivatives of the claimed invention is impossible as well.

Finally, a third theoretical method of obtaining harringtonine derivatives, involving the direct coupling of a linear sidechain with the alkaloid block, is to couple a linear α-hydroxy acid. However, this method is also impossible when R_1 and R_2 are free hydroxyls. (*See* Exhibit 2 of Wang II).

Thus, none of the cited references disclose the coupling of a linear sidechain to the cephalotaxine moiety when the sidechain bears a free alcohol, because it is chemically impossible. The esterification of alkaloid moieties with a linear branched sidechain is definitively impossible using the routes disclosed in the cited references. Further, the subsequent hydroxyalkylation of the intermediate ketoester results invariably in a non-separable mixture of diastereoisomers (see Wang II). Neither the coupling with a linear branched sidechain with the alkaloid moiety, nor the subsequent cyclization, of the claimed invention exist in the cited references. Thus, the claimed invention is neither taught nor suggested by the cited references. In fact, to the skilled artisan reading the cited references, the claimed invention would appear to be counter-intuitive, because it is impossible to create the claimed invention using the disclosures of the cited references.

In light of these remarks, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions to that prosecution of this application may be expedited.

Respectfully submitted,

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